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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/659,519

09/09/2003

David Sidransky

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6054

7590 09/27/2007  
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EXAMINER
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SALMON, KATHERINE D

ART UNIT	PAPER NUMBER
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1634

MAIL DATE	DELIVERY MODE
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09/27/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Advisory Action  
Before the Filing of an Appeal Brief**

Application No.

10/659,519

Applicant(s)

SIDRANSKY ET AL.

Examiner

Katherine Salmon

Art Unit

1634

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 12 September 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.  
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☒ The Notice of Appeal was filed on 09/12/2007. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ They raise the issue of new matter (see NOTE below);  
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See Continuation Sheet. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: \_\_\_\_\_.  
Claim(s) objected to: \_\_\_\_\_.  
Claim(s) rejected: 12-19.  
Claim(s) withdrawn from consideration: 20-24.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.  
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_.  
13. ☐ Other: \_\_\_\_\_.

/Jehanne Sitton/  
Primary Examiner  
9/19/2007

Continuation of 3. NOTE: The amendments to the claims are not being entered because the amendments to the claims raise new issues that would require further search and consideration. Whereas the claims previous required the amplification of a truncated p16 gene and the hypermethylation of a 5' ALT promoter region, the currently amended claims require an amplified product that encodes a truncated p16 gene product lacking exon 1 and hypermethylation of a 5' CpG island in the first exon of the p16 gene. The amendments to the claims recite steps which raise new issues under 35 USC 112 that would require further search and consideration.

Continuation of 11. does NOT place the application in condition for allowance because: The reply traverses the rejections of record. These arguments have been thoroughly considered but have not been found persuasive.

The reply asserts that the amendments to the claims remove the 35 USC 112, second paragraph rejection (p. 5 of reply). This argument is not persuasive because the arguments relates to limitations that are not recited in the claims in view of the non-entry of the afterfinal amendment.

The reply asserts that the claims have been amended to include elements that are clearly defined in the specification (P. 6) so that the rejection of new matter under 35 USC 112/first paragraph is moot. This argument is not persuasive because the arguments relates to limitations that are not recited in the claims in view of the non-entry of the afterfinal amendment.

With regard to the rejections made under 35 USC 112/ first paragraph scope of enablement, the reply traverses the rejection. The reply asserts that the specification provides guidance to differentiating p16 products by detecting p16 sequences lacking exon 1 but retaining exon 2 (p. 7 3rd paragraph). This argument is not persuasive because the argument relates to limitations (e.g. p16 gene product lacking exon 1) that are not recited in the claims in view of the non-entry of the afterfinal amendment.

The reply asserts that the demethylation agent can be used at any time to detect the differences in the cells (p. 7 last paragraph and p. 8 1st paragraph). The reply asserts that Claim 13 shows that if demethylation results in the second amplification product being detected it is due to the methylation of the 5'CpG island in the first exon where the effect of such methylation results in a truncated p16 gene product lacking exon 1 (p. 8 2nd paragraph). However, the amendment to the claims have not been entered and therefore it is still unpredictable that demethylation would show that there is a truncated p16 gene because the claims are still drawn to amplification of any region of the exon2 and exon 1 regions for detection of hypermethylation of the 5' ALT promoter of the p16 gene.

The reply asserts that it is hypermethylation of the first exon 5' CpG island that is associated with transcriptional repression (p. 8 2nd full paragraph). However, the claims are not drawn to the detection of the hypermethylation of a 5' CpG island in the first exon of the p16 gene because these limitations relate to limitations that are not recited in the claims in view of the non-entry of the afterfinal amendment. The reply asserts that the claims embrace reversal of truncation by demethylation that is associated with neoplastic cells (p. 8 3rd paragraph). However, the claims are drawn to the detection of any part of exon 1 and exon 2 and therefore it is not clear that the detection of any part of exon 1 and exon 2 is correlative to detecting of methylation. Rather, it is the detection of an amplification product of exon 2 without the amplification of exon 1 region and wherein there is detection of exon 1 when demethylation agent is added to the sample that detects the methylation of a p16 gene.

The reply asserts that specification provides many examples of detection of methylation (p. 9 last two paragraphs). The claims are drawn to the detection of the absence of any part of exon 1 with methylation, however the specification only shows a pattern of the absence of a specific region of exon 1 is correlated to hypermethylation. The claimed method is drawn to the association of every possible neoplasm with detection of methylation, however, the specification shows that in some instances exon 2 is absent in methylated tissue not exon 1. Yates et al. (Oncogene 2006 Vol. 25 p. 1984) shows that methylation is not only associated with neoplasm but is present in normal aged cells (p. 13-14 of final rejection).

Therefore the claims as pending are broad and the specification has not provided guidance to detect methylation by amplification of any part of the region of exon 1 and 2. To use the invention as presented would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Katherine Salmon

Examiner

Art Unit 1634